Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from -N(R^3)CO-, (where R^3 is a hydrogen atom or a straight or branched alkyl group); -N(R^3) SO_2-, -N(R^3)C(O)O- or -N(R^3)CON(R^{3a})- (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, C_{3-10} cycloaliphatic or C_{7-10} polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof.

REMARKS

Reconsideration of the present application in view of the above amendments and following remarks is requested respectfully.

Claims 1 and 5 to 19 are pending. Claims 1, 12, and 14 have been amended. No claims have been added or canceled. Applicants acknowledge and appreciate the Examiner's favorable ruling that the claims are patentable over the closest prior art, and that claim 12 defines allowable subject matter.

In response to the Requirement For Restriction mailed on January 29, 2001, Applicants elected for prosecution Group II, which is drawn to a compound of formula (Ia) wherein R^1 is an optionally substituted pyridyl, a method of treating diseases comprising

administering a compound of formula (Ia) wherein R^1 is an optionally substituted pyridyl, a method of inhibiting α4 integrin binding to, for example, α4β7 and α4β1 ligands comprising administering a compound of formula (Ia) wherein R^1 is an optionally substituted pyridyl, and pharmaceutical compositions comprising a compound of formula (Ia) wherein R^1 is an optionally substituted pyridyl. Amendments have been made to the claims to reflect this election. These amendments include defining R^1 as pyridyl in claims 1 and 14, and removing the proviso from these claims as phenyl is no longer recited in the definition of R^1.

The present Office Action contains rejections under 112, first and second paragraph, and as well as a Markush objection, which are discussed below.

Discussion of the Rejection Under Section 112, first paragraph

Claim 1 has been rejected as allegedly containing subject matter not described in such a way as to enable one skilled in the art to make and use the claimed compounds. Applicants respectfully request reconsideration of this rejection as the Office Action fails to establish that it would take anything more than routine experimentation to practice the present invention.

It is well-established that the first paragraph of Section 112 of the patent statute requires only objective enablement of the invention. How the teaching is set forth, either by the use of specific examples or broad terminology, is of no importance. *In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971). Accordingly, when rejecting a claim under the enablement requirement, it

is the PTO who bears the initial burden of setting forth technical reasoning as to why it is believed that the scope of protection is not adequately enabled. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *Id.*

Applying these tenets to the present situation, it is respectfully submitted that the present Office Action provides no such technical reasoning to support the opinion that Applicants have not enabled the compounds of claim 1. In fact, the *only* reasoning provided in the Office Action is the unsupported conclusion that "[t]he claims as recited are broader than the scope of enablement." Mere statements, however, are insufficient to compel a conclusion of nonenablement. *In re Colianni*, 668 F.2d 1229 (C.C.P.A. 1982). The statements must be supported by objective evidence. *Id.*

Significantly, the Office Action concedes that certain groups recited in the definitions of Alk^1, Alk^2, and R^4 are enabled. Applicants respectfully submit that in view of the substantial teachings in the specification, one of ordinary skill in the art could practice the additional group embodied in claim 1. For example, the Office Action concedes that compounds of formula (Ia) wherein Alk^1 is a branched aliphatic chain are enabled. Applicants respectfully submit that additional compounds wherein Alk^1 is defined as other aliphatic chains, as well as heteroaliphatic chains, may be obtained based on the teachings provided on, for example, page 9 of the specification. Indeed, the wide availability of diverse chemical compounds supports this conclusion, as suitable starting materials wherein Alk^1 is ethyl, hydroxymethyl, and aminoethyl

are well-known. *See*, for example, the Chemical Abstract pages included herewith. Moreover, additional Alk^1 groups embodied in claim 1 may be obtained through modification of such starting materials by the methods provided, for example, on pages 18, line 20 to page 19, line 22, or in the working examples.

Similarly, the Office Action concedes that compounds of formula (Ia) wherein Alk^2 is CH_2 are enabled. Applicants respectfully submit that additional compounds wherein Alk^2 is other aliphatic chains may be obtained based on the teachings provided on, for example, page 8, lines 28 to 30, of the specification. Applicants are at a loss to understand how the Office Action can reasonably conclude that compounds of claim 1 wherein Alk^2 is methylene are enabled, but compounds wherein Alk^2 is homologous aliphatic chains such as ethylene and propylene are not enabled, without a credible basis for reaching this conclusion. Particularly, in view of the fact that starting materials that may be used to prepare compounds of formula (Ia) wherein Alk^2 is, for example, ethyl and propyl, are well-known. *See*, for example, the Chemical Abstract pages included herewith. Thus, despite the comments in the Office Action, the skilled artisan would have no difficulty obtaining the additional Alk^2 groups embodied in claim 1.

It appears that the reasoning in the Office Action is that if certain species are not embodied in the working examples, they are *per se* not enabled. It is respectfully submitted, however, that the examples are set forth in the specification to provide support for the claims, not to provide the Patent Office with limitations to be read into the claims. For a claimed genus, representative examples, together with a statement applicable to the genus as a whole, will

ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in the same manner without undue experimentation. M.P.E.P. § 2164.02.

For example, the full scope of the variable R^4, including aliphatic, cycloaliphatic, and polycycloaliphatic groups are enabled as Applicants have provided representative working examples of *all three classes*. In this connection, Applicants respectfully direct the Examiner's attention to Example 5 on page 26 (wherein R^4 is an aliphatic isoproyl group); Example 6 on page 27 (wherein R^4 is a cycloaliphatic cyclopentyl group); and Example 32 on page 35 (wherein R^4 is a polycycloaliphatic adamantyl group). As for the remaining groups embodied by R^4, as noted above, the application is not silent as to certain embodiments simply because they are not set forth as working examples. Such a characterization misinterprets the present invention and fails to consider the *genus as a whole*, as is required by law. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Because the Office Action fails to provide any objective evidence that it would take anything more than routine experimentation to make and use the compounds provided in claim 1, and because such evidence is required to support the rejection of claim 1 under Section 112, first paragraph, Applicants respectfully request reconsideration and withdrawal thereof.

The Office Action also contains a rejection under Section 112, first paragraph, of claim 14. Applicants respectfully submit that the foregoing amendments to claim 14 render this rejection moot.

Claim 15 stand rejection under Section 112, first paragraph, as allegedly not enabling the specific diseases enumerated in the claim. Applicants respectfully submit, however, that in view

of the substantial teachings in the specification, the prevention of the enumerated diseases is, in fact, enabled. In this connection, Applicants teach that control of the physical interaction of inflammatory leukocytes with each other as well, as with other cell types, plays an important role in the regulation of immune and inflammatory responses and that these interactions are mediated by specific cell surface molecules including integrins. *See*, for example, page 1, lines 8 to 13 of the specification. Applicants also teach that in one particular subgroup of integrins, the α4 integrins, there is clear evidence that α4β1 (VLA-4) binds to an adhesion molecule known as VCAM-1, which is frequently up-regulated at sites of inflammation. *See*, for example, page 2, lines 18 to 21 of the specification.

Thus, it would be expected by one of ordinary skill in the art that if a VLA-4 inhibitor is given prior to a disease developing, the necessary integrin mediated interactions that lead to the disease are prevented, hence providing a method of prophylaxis. In this connection, Applicants cite the findings of Abraham, et al., *J. Clin. Invest.*, 93, 776 (1994) on page 2, lines 28 to 29 of the specification, who showed that prophylactic treatment of sheep with an anti-α4 monoclonal antibody prior to antigen challenge inhibits the late-phase increase in specific lung resistance. Given these findings, one would also expect that administration of a small molecule inhibitor of VLA-4 prior to the development of any clinical symptoms would also have a prophylactic effect. Significantly, the Office Action provides no objective evidence suggesting otherwise.

As noted above, the initial burden of setting forth sound, technical reasoning as to why it is believed that the scope of protection is not adequately enabled lies with the PTO. Rather than

providing such reasoning, however, the Office Action summarily states that "there is no known cure in the art for multiple sclerosis" (MS). This fact, however, even if true, is of no moment because Applicants need not provide a cure for multiple sclerosis for claim 15 to be enabled. To the contrary, claim 15 (which depends on claim 14) is directed to a method for the prophylaxis or treatment of certain diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role in a mammal, which comprises administering to a mammal suffering from such a disease or disorder a therapeutically effective amount of a compound of formula (1).

Applicants respectfully submit that one of ordinary skill in the art would expect compounds of formula (I) to be of use in the prophylaxis and treatment of MS. In this connection, Applicants respectfully refer the Examiner to the findings of Yednock, *Nature*, 356, 63 (1992) (copy included herewith), cited by Applicants on page 2, lines 27 of the specification, which demonstrates that in an MS animal model (experimental autoimmune encephalomyelitis (EAE)) antibodies against VLA-4 are effective in prevention of EAE.

Applicants respectfully point out that there is no requirement in the patent laws that a patent specification address all potential problems that might be encountered in practicing an invention. To the contrary, it is improper for the PTO to require any showing regarding the degree of effectiveness of therapeutic inventions, such as those now claimed. M.P.E.P. § 2107.02; *In re Sichert,* 566 F.2d 1154 (C.C.P.A. 1977). Thus, even assuming, *arguendo*, that Applicants do not provide a cure for MS, this fact alone would not negate the patentablility of claim 15. To the contrary, Applicants have provided, for example, on page 37, line 18 to page

39, line 19 of the specification, assays that may be used to determine biological activity and specificity together with the levels for activity that are preferably obtained for the compounds to be suitable for the claimed use. Because the Office Action provides no credible reason for doubting that compounds possessing activity would be useful in treating MS (or, for that matter, any of the additional diseases recited in claim 15), Applicants respectfully request reconsideration and withdrawal of the rejection under Section 112, first paragraph.

Discussion of the Rejection Under Section 112, second paragraph

The Office Action includes various objections to the form of Applicants' claims accompanied by a statement that the claims are indefinite. Specifically, the Office Action objects to the use of the terms "substituted aliphatic," "heteroaliphatic chain," "optionally substituted aliphatic," "cycloaliphatic," and "polycycloaliphatic group" in claim 1, and "cycloaliphatic," "aromatic," "heteroaromatic," "polycycloaliphatic," and "polyheterocycloaliphatic" in claim 14. With respect to the terms "aromatic," "heteroaromatic," and "polyheterocycloaliphatic," Applicants believe the foregoing amendments to claims 1 and 14 render the rejection moot. With respect to the remaining terms, it is submitted respectfully that one of ordinary skill in the art would have no difficulty in understanding the metes and bounds of these claims and the terminology used therein, as they are both clear and definite.

It is asserted in the Office Action that the scope of the above terms is so broad as to be "virtually meaningless." Applicants respectfully disagree and submit that the Office Action

confuses breadth with indefiniteness. It is unclear how these terms could be "meaningless" when Applicants have provided precise definitions for these terms on, for example, pages 9 and 11 of the specification. Applicants define these terms in a manner that one of ordinary skill in the art would appreciate, which is all that is required to satisfy 35 U.S.C. §112, second paragraph.

Nevertheless, in an effort to address the Examiner's concerns, the term "aliphatic" has been amended to include a C_{1-6} carbon range. Support for this amendment is provided, for example, on page 9, lines 1 to 4 of the specification. The term "heteroaliphatic" has been replaced by the term "C_{1-6} heteroaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups." Support for this amendment is provided, for example, on page 9, lines 6 to 8 of the specification. The term "cycloaliphatic" has been amended to include a C_{3-10} carbon range. Support for this amendment is provided, for example, on page 10, lines 8 to 12 of the specification. The term "polycycloaliphatic" has been amended to include a C_{7-10} carbon range. Support for this amendment is provided on page 10, lines 19 to 24 of the specification. The amended claims are believed to be of a scope equivalent to the scope of the originally filed claims, but now contain information as to both the ring size and nature of the heteroatoms recited in claims 1 and 14.

With respect to the terms "substituted" and "optionally substituted," Applicants respectfully submit that the nature and identity of the substituents would be well-understood by one of ordinary skill in the art when armed with the teachings provided in the specification. Indeed, the specification provides the identity of exemplary substituent groups and the skilled

artisan would appreciate the meaning of these terms. As such, further explanation is unnecessary. Accordingly, Applicants request respectfully the withdrawal of the rejection under Section 112, second paragraph.

Discussion of the Markush Rejection

Claims 1 and 14 stand rejected, in part, as allegedly being drawn to an improper Markush group. Applicants respectfully request clarification concerning this objection, however, as the Office Action fails to point out which Markush group serves as the basis of the objection. As best understood, the Office Action appears to object generally to the compound of formula I as allegedly lacking what the Office Action terms a "common nucleus."

In this connection, Applicants respectfully point out that the invention lies in the provision of novel *phenylalanine derivatives* possessing similar biological activity. Numerous working examples are set forth, for example, on pages 25 to 36 of the specification, each of which contains a phenylalanine "common nucleus" as defined in the present claims. Thus, despite the assertions in the Office Action, Applicants have shown that the compounds, when considered as a whole, are not so diverse that they demonstrate dissimilar or unrelated properties. Moreover, Applicants have now amended claim 1 to define R^1 as an optionally substituted pyridyl group, further defining the "common nucleus" of the compounds of formula I.[1] Under

[1] It is Applicants' understanding that a prior art search was performed on the compound of formula I prior to the present amendment, supporting Applicants' position that the

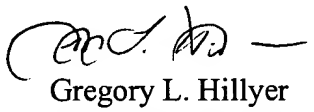
such circumstances, Applicants respectfully request withdrawal of the Markush objection to claims 1 and 14.

Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action on the merits is requested respectfully.

Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,



Gregory L. Hillyer
Registration No. 44,154

Date: September 25, 2001
WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100

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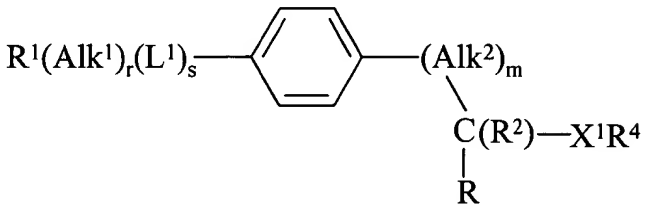
compounds of Formula I contained a common structural element.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 12, and 14 have been amended as follows:

1. (amended twice) A compound of formula (1a):



(1a)

wherein:

R is a carboxylic acid;

R^1 is an optionally substituted pyridyl [phenyl, pyridyl, or pyrimidinyl] group;

Alk^1 is an optionally substituted C_{1-6} aliphatic chain or C_{1-6} heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups;

L^1 is a linker atom or group;

r and s, which may be the same or different, is each zero or an integer 1;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from $-N(R^3)CO-$, (where R^3 is a hydrogen atom or a straight or

branched alkyl group); -N(R^3) SO_2-, -N(R^3)C(O)O- or -N(R^3)CON(R^{3a})- (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, C_{3-10} cycloaliphatic or C_{7-10} polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof. [;

with the provisos that:

when R^1 is unsubstituted phenyl, -$(Alk^1)_r(L^1)_2$- is a -CONH- group, Alk^2 is -CH_2-, m is an integer 1, R^2 is a hydrogen atom, and X^1 is a -NHC(O)O- group, R^4 is not a t-butyl group;

when R^1 is unsubstituted phenyl, -$(Alk^1)_r(L^1)_2$- is a -CONH- group, Alk^2 is -CH_2-, m is an integer 1, R^2 is a hydrogen atom, and X^1 is a -NHC(O)- group, R^4 is not a 1-[(phenylmethoxy)carbonylamino]isobutyl group; and

when R^1 is 2-(trifluoromethyl)phenyl, -$(Alk^1)_r(L^1)_2$- is a -CONH- group, Alk^2 is -CH_2-, m is an integer 1, R^2 is a hydrogen atom, and X^1 is a -NHC(O)- group, R^4 is not a 4-[[[(t-butyloxy)carbonyl]amino]methyl]cyclohexyl group.]

12. (amended once) A compound which is:

N-Isopropaloyl-*N*-(3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine;

N-Cyclopropaloyl-*N*-(3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine;

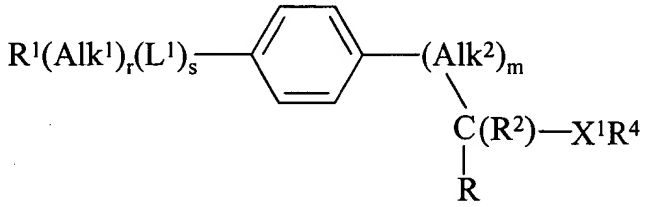
N-Acetyl-*N'*-(3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine;

[*N*-(Trimethylacetyl)-*N'*-(2,6-difluorobenzoyl)-*L*-4-aminophenylalanine;

N-(1-Adamantylcarbonyl)-*N'*-(2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine;]

and the salts, solvates, hydrates and N-oxides thereof.

14. (amended once) A method for the prophylaxis or treatment of a disease or disorder involving inflammation in which the extravasation of leukocytes plays a role in a mammal, which comprises administering to a mammal suffering from such a[s] disease or disorder a therapeutically effective amount of a compound of formula (1):



(1)

wherein:

R is a carboxylic acid (CO_2H) [or a derivative thereof];

R^1 is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally substituted [cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;] pyridyl group;

Alk^1 is an optionally substituted C_{1-6} aliphatic chain or C_{1-6} heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups;

L^1 is a linker atom or group;

r and s, which may be the same or different, is each zero or an integer 1 provided that

when r is zero R^1 is an optionally substituted [cycloaliphatic, polycyloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic] pyridyl group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from $-N(R^3)CO-$, (where R^3 is a hydrogen atom or a straight or branched alkyl group); $-N(R^3)SO_2-$, $-N(R^3)C(O)O-$ or $-N(R^3)CON(R^{3a})-$ (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, C_{3-10} cycloaliphatic or C_{7-10} polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof.